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ORIGINAL PAPER

Effects of single therapeutic doses of promethazine, fexofenadine and olopatadine on psychomotor function and histamine-induced wheal- and flare-responses: a randomized double-blind, placebo-controlled study in healthy volunteers

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Abstract Since most first-generation antihistamines have undesirable sedative effects on the central nervous systems (CNS), newer (second-generation) antihistamines have been developed to improve patients' quality of life. However, there are few reports that directly compare the antihistaminic efficacy and impairment of psychomotor functions. We designed a double-blind, placebo controlled, crossover study to concurrently compare the clinical effectiveness of promethazine, a first-generation antihistamine, and fexofenadine and olopatadine, second-generation antihistamines, by measuring their potency as peripheral inhibitors of histamine-induced wheal and flare. Further, we investigated their sedative effects on the CNS using a battery of psychomotor tests. When single therapeutic doses of fexofenadine (60 mg), olopatadine (5 mg) and promethazine (25 mg) were given in a double-blind manner to 24 healthy volunteers, all antihistamines produced a significant reduction in the wheal and flare responses induced by histamine. In the comparison among antihistamines, olopatadine showed a rapid inhibitory effect compared with fexofenadine and promethazine, and had a potent effect compared with promethazine. In a battery of psychomotor assessments using critical flicker fusion, choice reaction time, compensatory tracking, rapid visual information processing and a line analogue rating scale as a subjective assessment of sedation, promethazine significantly impaired psychomotor function. Fexofenadine and olopatadine had no significant effect in any of the psychomotor tests. Promethazine, fexofenadine and olopatadine did not affect behavioral activity, as measured by wrist actigraphy. These results suggest that olopatadine at a therapeutic dose has greater antihistaminergic activity than promethazine, and olopatadine and fexofenadine did not cause cognitive or psychomotor impairment.

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Introduction

Antagonists of histamine H_1 receptors, antihistamines have been widely used for the treatment of seasonal and perennial allergic rhinitis and chronic idiopathic urticaria. Classical (first-generation) antihistamines such as *d*-chlorpheniramine, diphenhydramine and promethazine, however, have undesirable side effects including sedation, at therapeutic doses [8, 27, 30]. Sedation induced by antihistamines impairs cognitive and psychomotor functions [13, 24, 39]. Notably, daytime sedation disturbs the ability to work, and excessive sedation reduces the patient's compliance with treatment regimens [25].

The sedative effect of antihistamines on the central nervous system (CNS) is due to their ability to cross the blood–brain barrier and to block histamine neurotransmission through central histamine H_1 receptors. In fact, first-generation antihistamines have been shown to occupy a large proportion of histamine H_1 receptors in the human brain by positron emission tomography (PET) [41]. A number of newer (second-generation) antihistamines, which do not readily cross the blood–brain barrier, have been developed to relieve side effects on the CNS and to improve quality of life [22, 32, 36]. The second-generation antihistamines fexofenadine and olopatadine, which have potent antihistaminic properties and fewer CNS side effects, are now widely used to treat seasonal allergic rhinitis in Japan. Fexofenadine and olopatadine have been approved in Japan for the treatment of allergic disorders at a recommended total daily dose of 120 mg (60 mg twice daily) and 10 mg (5 mg twice daily), respectively. In healthy volunteers, fexofenadine did not have any disruptive effects on psychomotor or cognitive performance, when administered at doses of up to 360 mg [9, 10, 14]. On the other hand, olopatadine at 10 mg, which is double the standard oral dose, caused a decrease in behavioral activity as measured by wrist actigraphy, although it did not affect psychomotor/cognitive performance [14]. However, further comparative studies should be carried out to determine the clinical profile of antihistamines in terms of the relationship between their efficacy (antihistaminic activity; benefit) and psychomotor functions (risk) using the therapeutic doses. The efficacy of antihistamines has been evaluated with histamine challenge tests using iontophoresis [29]. Iontophoresis is a non-invasive method of histamine application to induce an inflammatory skin response (wheal/flare), which is useful to compare the effects of antihistamines.

Thus, this study was designed to investigate the effects of fexofenadine, olopatadine and promethazine, a positive control, at the single therapeutic doses on psychomotor/cognitive function and on histamine-induced cutaneous responses in healthy Japanese.

Materials and methods

Subjects

The present study was approved by the institutional review board of the Medical School Hospital of Nagoya University (an approval number: 208008).

All subjects were given written informed consent with respect to their participation in the study. Twenty-four healthy Japanese volunteers (twelve females, twelve males) aged between 18 and 22 (mean ± SE: 19.3 ± 0.3) years were entered into the study. None of the subjects had evidence of previous or current physical and mental illness, including allergies, on the basis of medical history, a clinical examination, a 12-lead electrocardiogram, and standard laboratory tests of plasma and urine. None had a history of alcohol or drug abuse or drug allergy. Subjects received no medication for 2 weeks before and during the study.

Study design and treatments

The study was a randomized, double-blind, placebo-controlled, crossover study with four periods of treatment each separated by a washout period of 7 days. During each period, subjects received a single therapeutic dose of each of the study drugs: promethazine (25 mg), a first-generation antihistamine, and fexofenadine (60 mg) and olopatadine (5 mg), second-generation antihistamines, and placebo. The study drugs were assigned according to the randomization list. All treatments were supplied in capsules, which were identically matched in size, color and shape to respect the double-blind nature of the study. The study drugs were administered with about 150 ml of water. The Pharmacokinetic parameters of promethazine (25 mg) [20], fexofenadine (60 mg) [33] and olopatadine (5 mg) [5] are as follows: T(max) of them are 2.7, 2.2 and 1.0 h, T(1/2) of them are 12.7, 9.6 and 8.8 h, respectively.

Procedures

The examination was performed over 4 weeks at intervals of 1 week. Subjects attended the examination site on the day before each of the tests, where breath alcohol, health and medication were checked. The day before the first test,

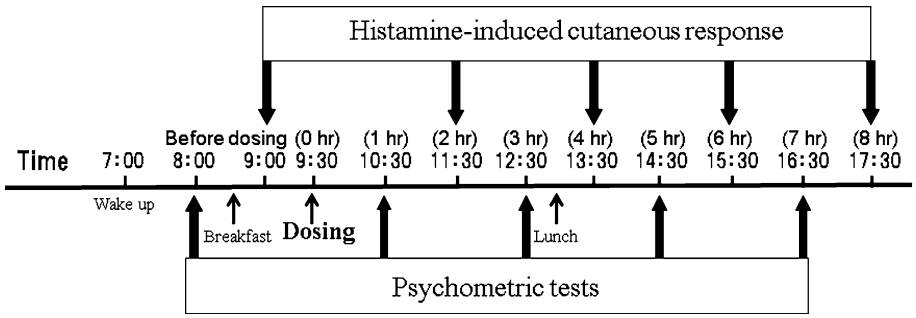

Fig. 1 Study schedule

they received sufficient training (at least three times) for the psychometric tests in order to eliminate the effects of learning [23]. At each visit, they were instructed to go to bed in a single room at a hotel near the examination site (Nagoya University Hospital) at 2300 hours.

The study schedule is shown in Fig. 1. On each of the test days, subjects were awakened at 0700 hours, and moved to the examination room. An alcohol breath test was first conducted. Two baseline measurements were undertaken before medication. First, at 0800 hours, subjects undertook a psychometric test. Second, at 0900 hours, subjects were assessed for a histamine-induced cutaneous response. Breakfast was taken between 0830 and 0900 hours. Study drugs were administered at 0930 hours. Then, the psychometric tests were carried out 1, 3, 5 and 7 h after the drug administration, and the histamine-induced cutaneous response was examined 2, 4, 6 and 8 h after the drug administration. The duration of each test in the psychometric test battery was for ~30 min.

The consumption of alcohol, nicotine, caffeine and grapefruit was prohibited for 2 days before and during testing. Food consumption was strictly controlled the night before and during testing. Adverse events and concomitant medications were recorded at each visit.

Assessments

Histamine-induced cutaneous response

Histamine iontophoresis-induced wheal- and flare-responses were measured, according to the method of Takahashi et al. [33]. Histamine dihydrochloride was dissolved in distilled water at a concentration of 10 mg/ml. The histamine solution was applied to the participant's forearm (alternating between the right and left sides) by an iontophoreser (UI-2060, BS Medical, Tokyo, Japan), with cotton wool. A constant current of 0.1 mA was applied for 1 min. The areas of histamine-induced wheal- and flare-response were assessed 15 min after the application via a planimetric evaluation, which was performed using NIH imaging computer software. The sizes of wheal- and flare- areas were expressed as a percentage of the baseline histamine response before the intake of the study drug.

Psychometric tests

Critical flicker fusion

Critical flicker fusion (CFF) was used as a means of measuring overall CNS arousal using the ability to discriminate discrete 'bits' of sensory information [7].The test device was composed of four light-emitting diodes arranged in a 1-cm square. The diodes were held in foveal fixation 1 m from the subject. The lights were flicked on and off at a constantly increasing or decreasing rate. Subjects were required to discriminate flicker from fusion, and vice versa. Individual thresholds were determined as the mean of each threshold in four ascending (flicker to fusion) and four descending (fusion to flicker) measurements.

Choice reaction time

The choice reaction time (CRT) was used as a sensitive measure of drug-induced changes in sensorimotor performance [6]. The test device was composed of a central starting button, six red buttons aligned in the shape of a fan, which were equally separated from the starting button, and corresponding response buttons located in front of each red light, and six green lights located behind each red light. Subjects placed the index finger of their preferred hand on the starting button and then were required to extinguish one of six equidistant red lights, illuminated at random, by touching the corresponding response button in front of the light as quickly as possible. The green light was used as notice indicator to let the subject know which of the red lights to focus on. The time between the red light coming on and the finger being released from the starting button was taken as a recognition reaction time of CRT. The mean reaction time for 48 stimulus presentations was recorded.

Compensatory tracking test

The compensatory tracking test (CTT) was used as a means to assess divided attention [11]. Subjects were required to keep a cursor in alignment with a moving target on a visual display unit screen using a mouse. The evaluation measure of this tracking task was the mean difference between the centers of the target and cursor in pixels, sampled 5 times per second, during the 9-min test period. Lower scores are indicative of more accurate tracking.

In addition, a peripheral awareness task is included in which the subject responds to a stimulus presented in the periphery of vision, while simultaneously attending to the tracking task described above. One hundred stimuli appear at different location, which randomly appear at four corners on the screen. Stimuli duration is 3 s, and stimuli interval is 3–6 s. Subjects should control the mouse to track the target, and simultaneously click the left side of mouse as soon as possible if they notice the stimuli at a corner on the screen. The mean reaction time to these stimuli over the trial period was taken as the response measure for this component of the divided attention task.

Rapid visual information processing

Rapid visual information processing (RVIP) was used as a means to assess attention performance [40]. Subjects were required to monitor a series of single digits (0–9) appearing on the screen at a rate of 100 digits every minute and respond to consecutive sequences of three odd or even digits using a mouse button during the 9-min test period. The evaluation measures are the number of correct responses. The RVIP task was performed only at baseline and 3 h after the administration of study drugs. This task was followed by the CFF, the CRT and the CTT at baseline and 3 h after the administration of study drugs. Because this task requires high concentration for 9 min and is mentally taxing to subjects, the RVIP task is done only twice a day.

Line analogue rating scale

The line analogue rating scale (LARS) was employed as a measure of the subjective effects of psychoactive drugs [6]. Subjects were required to mark a point, which represented how they felt, on 100-mm line analogue scales. Subjects should mark degree of feeling tiredness, drowsiness and alertness using this scale which was defined that values 0 showed that they feel no tiredness, no drowsiness, and are not alert, value 100 showed that they feel very tired, very drowsy, and are very alert. The mean score of the rating of 'tiredness', 'drowsiness' and 'not alert' was taken as a measurement of sedation [10].

Wrist actigraphy

Actigraphy has been shown to be capable of measuring reductions in behavioral activity (sedation) caused by psychoactive drugs [31]. On each test day, a watch-type wrist actigraph (Actiwatch, Cambridge Neurotechnology Ltd, UK) was placed on the wrist of subjects to detect three-dimensinal movements, and the behavioral activity of subjects was measured from 1-h pre-dose to 7-h post-dose. The wrist actigraph contained a piezoelectric transducer that detects motion in all three axes and generates a signal voltage. In the zero crossing mode, each crossing of the reference voltage during an epoch is counted, which gives a measure of the frequency but not the intensity (amplitude) of the movements. Mean behavioral activity over the entire recording period was automatically calculated for % sleep-like behavior using ACTION3 software and its validated sleep/wake algorithm (Ambulatory Monitoring Inc, USA).

Statistical analysis

The data were analyzed using the one-way ANOVA or two-factor factorial ANOVA, followed by Tukey–Kramer test, regarding changes from baseline measurements. The one-way ANOVA was used for the RVIP test, and two-factor factorial ANOVA was used for the histamine-induced cutaneous response (wheals and flare) and the psychomotor tests such as CFF, CRT, CTT, actigraphy, and LARS. The factors of two-factor factorial ANOVA were treatment (4 levels: placebo, promethazine, fexofenadine and olopatadine) and time (4 levels: histamine-induced cutaneous response; 2, 4, 6 and 8 h, psychometric tests; 1, 3, 5 and 7 h). In the post hoc pairwise comparisons between the treatment means, Tukey–Kramer test was used for the histamine-induced cutaneous response (wheals and flare) and the psychomotor tests such as CFF, CRT, CTT, RVIP, and LARS. In order to ensure that there were no significant differences across tasks and conditions at pre-treatment, baseline statistical analyses were conducted and used for comparison to post-treatment results. A P value of <0.05 was defined as statistically significant.

Results

Histamine-induced cutaneous response

All 24 subjects completed the four periods of the study.

Histamine iontophoresis produced a marked wheal- and flare-response accompanied by itching. There was no difference in baseline data for the wheal and flare components of the histamine-induced cutaneous response among the treatment groups.

The effects of antihistamines on wheals induced by the histamine application are shown in Fig. 2a. The two-factor ANOVA showed a significant main effect for treatment [F (3, 276) = 12.36, $P < 0.01$], time [F (3, 276) = 8.06, $P < 0.01$] and interaction between treatment and time [F (9, 276) = 1.96, $P < 0.05$]. Post hoc pair-wise comparisons showed that fexofenadine ($P < 0.01$) and olopatadine ($P < 0.01$) overall had a significantly greater inhibitory effect on wheals than did the placebo. Analysis of the time course showed significant inhibition with promethazine in comparison to placebo, only at 4-h post-dose. The inhibitory effect of fexofenadine was significantly different from that of placebo at 4- and 8-h post-dose. Olopatadine had a significant effect on wheals in comparison to placebo and promethazine at 2-, 4-, 6- and 8-h post-dose. Promethazine, fexofenadine and olopatadine caused maximum inhibition at 4 h, i.e., 52, 80 and 99% of the baseline level, respectively. The marked inhibition of wheals by olopatadine continued during 4 and 8 h. The area under the effect curve (AUC) for changes from baseline was used to assess the overall effect of the treatment. AUC from baseline to the last assessment was calculated using the trapezoidal rule. As shown in the upper graph in Fig. 2a, a one-way ANOVA of the effects of antihistamines on wheals induced by the histamine application, showed a significant main effect for treatment [F (3, 92) = 13.03, $P < 0.01$]. Post hoc pair-wise comparisons showed that fexofenadine ($P < 0.05$) and olopatadine ($P < 0.05$) had a significantly greater inhibitory effect on wheals than the placebo. The inhibitory effect of olopatadine ($P < 0.05$) was significantly different from that of promethazine. There was no significant difference between olopatadine and fexofenadine in their inhibitory effects on wheals.

With regard to inhibition of the flaring reaction (Fig. 2b), a two-factor ANOVA showed a significant main effect for treatment [F (3, 276) = 7.79, $P < 0.01$] and time [F (3, 276) = 6.80, $P < 0.01$], although the effect of interaction between treatment and time was not significant [F (9, 276) = 0.65, $P = 0.75$]. Post hoc pair-wise comparisons showed that fexofenadine ($P < 0.01$) and olopatadine ($P < 0.01$) overall had a significantly greater inhibitory effect on flares than the placebo. Analysis of the time course showed a significant effect with promethazine in comparison to placebo, only at 4-h post-dose. The inhibitory effects of fexofenadine were significantly different from those of the placebo at 4, 6 and 8 h. The inhibitory effects of olopatadine were significantly different from those of the placebo at 2, 4, 6 and 8 h, and from promethazine at 4 h. The inhibitory effect of each drug on flares was similar to that on wheals. With analysis of AUC for changes from baseline, a one-way ANOVA of the effects of antihistamines on flares showed a significant main effect for treatment [F (3, 92) = 7.69, $P < 0.01$], as shown in the upper graph in Fig. 2b. Post hoc pair-wise comparisons showed that fexofenadine ($P < 0.05$) and

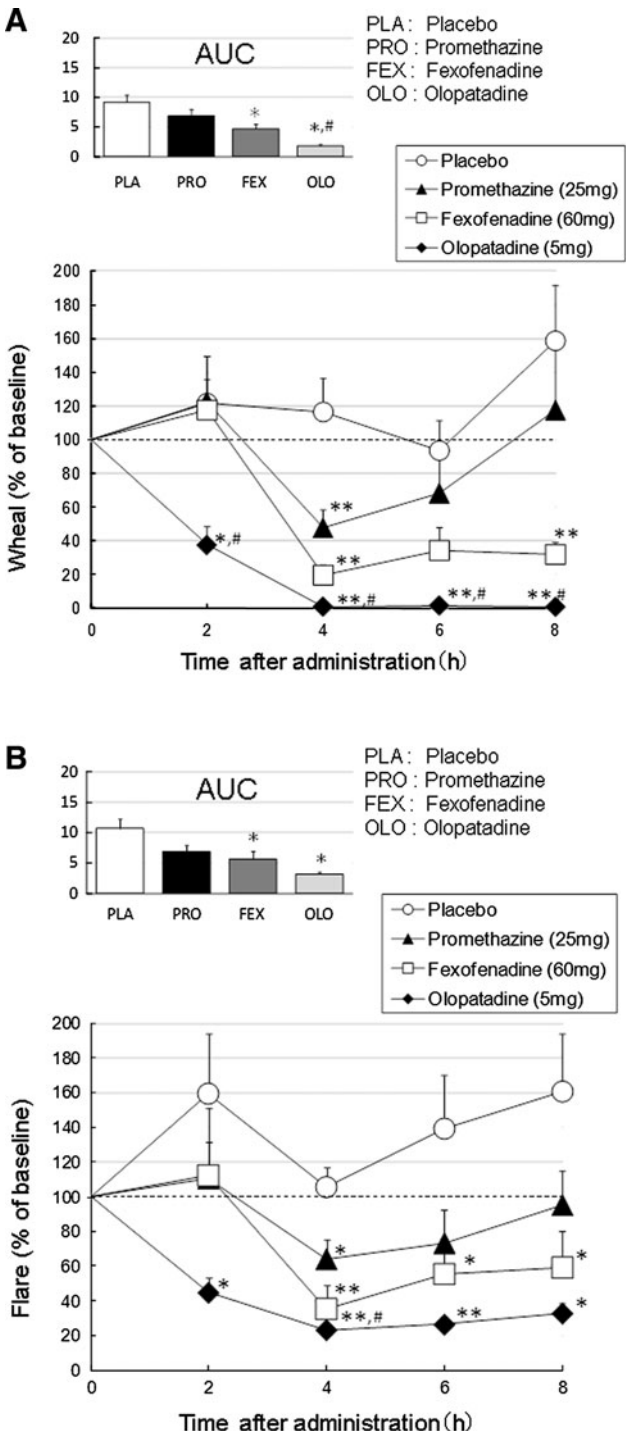

Fig. 2 Effects of antihistamines on histamine-induced wheal (**a**) and flare (**b**) responses. Each value is expressed as a percentage of the baseline, and is the mean ± SEM for 24 subjects. *Each upper graph* in **a** and **b** shows the corresponding area under the effect curve (AUC) for changes from baseline of wheal (**a**) and flare (**b**) responses. $^{*}P < 0.05$, $^{**}P < 0.01$ compared with placebo, $^{\#}P < 0.05$ compared with promethazine

olopatadine ($P < 0.05$) had significantly greater inhibitory effects on flares than the placebo. There was no significant difference between olopatadine and fexofenadine in their inhibitory effects on flares.

Assessment of cognitive and psychomotor function

There was no difference in baseline data for each psychometric parameter among the treatment groups. The effects of antihistamines on CFF, CRT, and CTT are shown in Fig. 3. The effects of antihistamines on RVIP, LARS and wrist actigraphy are shown in Fig. 4.

For the CFF test (Fig. 3a), a two-factor ANOVA showed a significant main effect of treatment [F (3, 276) = 5.62, $P < 0.01$], although the effect of time was not significant [F (3, 276) = 1.99, $P = 0.12$]. There was also significant interaction between treatment and time [F (9, 276) = 5.16, $P < 0.01$]. Post hoc pair-wise comparisons indicated that promethazine significantly reduced the CFF thresholds compared with placebo ($P < 0.01$), fexofenadine ($P < 0.01$) and olopatadine ($P < 0.01$). Analysis of the time course showed a significant decrease in CFF thresholds with promethazine in comparison to placebo and fexofenadine, at 3-, 5- and 7-h post-dose. The effects of promethazine were also significantly different from those of olopatadine at 5 h.

For the CRT test (Fig. 3b), a two-factor ANOVA showed a significant main effect of treatment [F (3, 276) = 11.11, $P < 0.01$], although the effect of time was not significant [F (3, 276) = 1.77, $P = 0.15$]. There was also a significant effect of interaction between treatment and time

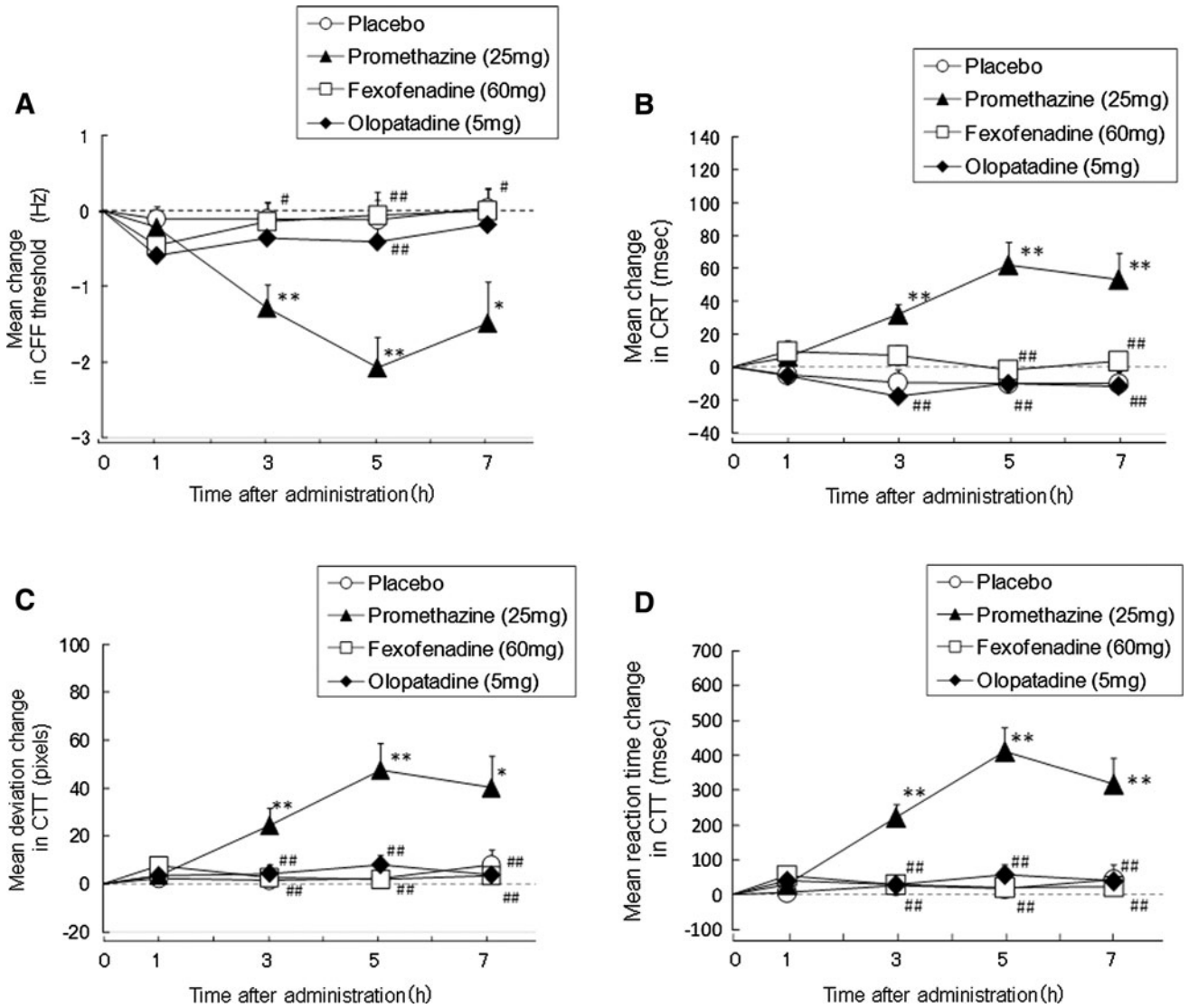

Fig. 3 Effects of antihistamines on CFF (**a**), CRT (**b**), tracking ability (**c**) and recognition reaction time (**d**) in the CTT. Each value represents the mean change from baseline, and is the mean ± SEM for 24 subjects. $^{*}P < 0.05$, $^{**}P < 0.01$ compared with placebo, $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ compared with promethazine

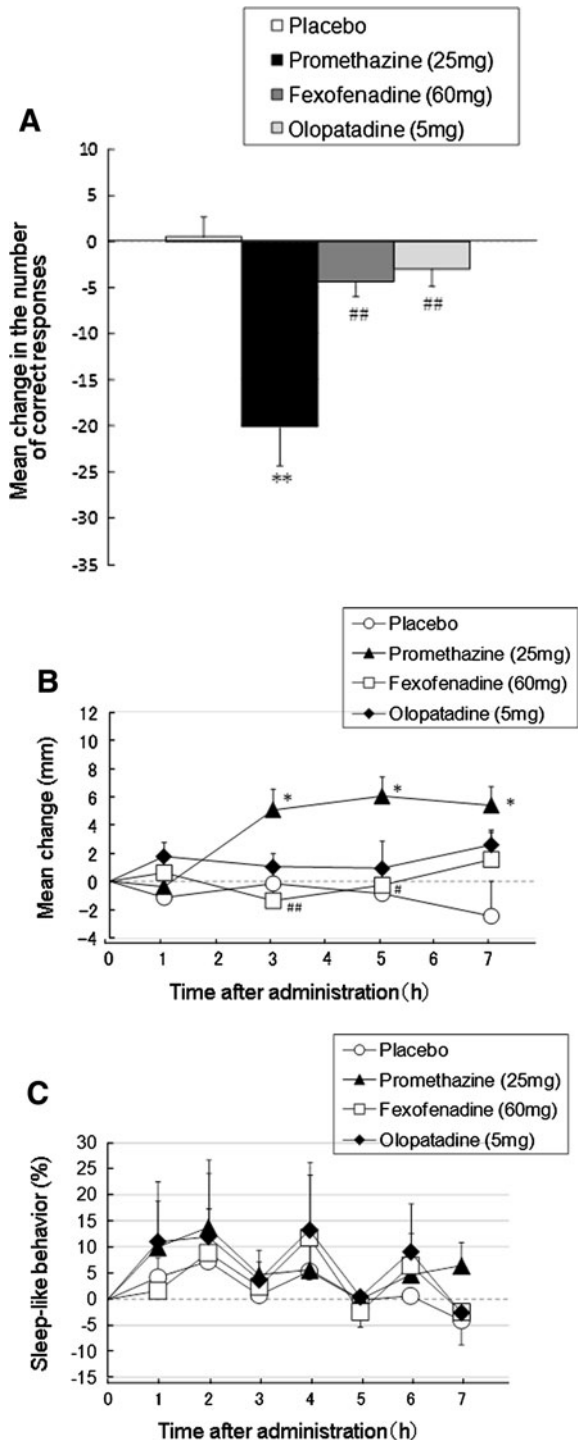

Fig. 4 Effects of antihistamines on RVIP task (**a**), sedation of LARS (**b**) and sleep-like activity measured by wrist actigraphy (**c**). Each value represents the mean change from baseline, and is the mean ± SEM for 24 subjects. $^{*}P < 0.05$, $^{**}P < 0.01$ compared with placebo, $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ compared with promethazine

[F (9, 276) = 5.13, $P < 0.01$]. Post hoc pair-wise comparisons indicated that promethazine significantly increased the response time compared with placebo ($P < 0.01$), fexofenadine ($P < 0.01$) and olopatadine ($P < 0.01$). Analysis of the time course showed a significant increase in the response time with promethazine in comparison to placebo and olopatadine, at 3-, 5- and 7-h post-dose. The effects of promethazine were also significantly different from those of fexofenadine at 5 and 7 h.

For the tracking task in the CTT test (Fig. 3c), a two-factor ANOVA showed a significant main effect for treatment [F (3, 276) = 9.18, $P < 0.01$], time [F (3, 276) = 6.09, $P < 0.01$] and interaction between treatment and time [F (9, 276) = 6.03, $P < 0.01$]. Post hoc pair-wise comparisons indicated that promethazine significantly impaired tracking ability compared with placebo ($P < 0.01$), fexofenadine ($P < 0.01$) and olopatadine ($P < 0.01$). Analysis of the time course showed a significant impairment in tracking ability with promethazine in comparison to placebo, fexofenadine and olopatadine, at 3-, 5- and 7-h post-dose.

For the peripheral awareness task in the CTT test (Fig. 3d), a two-factor ANOVA showed a significant main effect for treatment [F (3, 276) = 14.20, $P < 0.01$], time [F (3, 276) = 9.52, $P < 0.01$] and interaction between treatment and time [F (9, 276) = 9.73., $P < 0.01$]. Post hoc pair-wise comparisons indicated that promethazine significantly increased the response time in the periphery of vision compared with the placebo ($P < 0.01$), fexofenadine ($P < 0.01$) and olopatadine ($P < 0.01$). Analysis of the time course showed a significant increase in the response time with promethazine in comparison to placebo, fexofenadine and olopatadine, at 3-, 5- and 7-h post-dose.

For the RVIP test (Fig. 4a), a one-way ANOVA of correct responses showed a significant main effect for treatment [F (3, 92) = 12.27, $P < 0.01$]. Post hoc pair-wise comparisons indicated that promethazine significantly decreased the correct responses compared with the placebo ($P < 0.01$), fexofenadine ($P < 0.01$) and olopatadine ($P < 0.01$).

For the sedation score of LARS (Fig. 4b), a two-factor ANOVA showed a significant main effect of treatment [F (3, 276) = 4.12, $P < 0.01$], although the effect of time was not significant [F (3, 276) = 1.51, $P = 0.21$]. There was also a significant effect of interaction between treatment and time [F (9, 276) = 2.82, $P < 0.01$]. Post hoc pair-wise comparisons indicated that promethazine significantly increased the sedation score compared with placebo ($P < 0.05$). Analysis of the time course showed a significant increase in the sedation score with promethazine in comparison to placebo, at 3-, 5- and 7-h post-dose. The effects of promethazine were also significantly different from fexofenadine at 3- and 5-h post-dose.

A two-factor ANOVA of percentage sleep measured by wrist actigraphy revealed that there was no significant main effect for treatment [F (3, 552) = 0.71, $P = 0.55$] and the

effect of interaction between treatment and time [$F(3, 552) = 1.40$, $P = 0.13$]. The effect of time was significant [$F(3, 552) = 12.86$, $P < 0.01$] (Fig. 4c).

There were no serious adverse events and no subject withdrew due to drug intolerance or any drug-related adverse event.

Discussion

Second-generation antihistamines are differentiated from the first-generation antihistamines by their increased specificity and efficacy toward histamine H_1 receptors, and the low sedative effects due to their much lower penetration into the CNS. However, there are few reports that directly compare the antihistaminic efficacy and impairment of psychomotor functions. The aim of this study was to investigate the effects of fexofenadine and olopatadine on the CNS and their clinical effectiveness by measuring their activity as peripheral inhibitors of histamine-induced wheal and flare. Possible effects on the CNS were assessed using a battery of psychometric tests as shown by previous reports [10, 14].

In the present study, all antihistamines at single therapeutic dosages produced a significant reduction in the wheal and flare responses induced by histamine. Olopatadine showed a rapid and long-lasting inhibitory effect on the histamine-induced cutaneous response. Fexofenadine also had a long-lasting effect. Promethazine, however, had an effect that was less marked and only transient. The results for olopatadine and fexofenadine were consistent with a previous report [33, 34]. Further, consistent with a previous result [21], the inhibition of histamine-induced itching by olopatadine, but not by fexofenadine, paralleled the inhibitory effect on wheals (data not shown). The rapid effect of olopatadine is due to the fact that its blood concentration reaches a maximum 1 h after oral administration [5], while the time to reach the maximum blood concentration for promethazine [20] and fexofenadine [33] is 2.7 and 2.2 h, respectively. In addition, the potent and long-lasting effect of olopatadine is due to its non-competitive antagonist function to histamine H_1 receptors. Namely, the inhibitory effect of olopatadine on histamine receptors is little reduced in the presence of high levels of histamine because of noncompetitive antagonism [16]. These pharmacological and pharmacokinetic characteristics contribute to the clinical effectiveness of olopatadine in patients with seasonal allergic rhinitis [4]. It has been reported that olopatadine at 5 mg caused a marked improvement in nasal discharge and nasal congestion in Japanese patients with cedar pollinosis when they were exposed to cedar pollen in an environmental exposure unit, while fexofenadine at 60 mg did not [4]. These findings suggest that olopatadine is more effective than fexofenadine in improving nasal symptoms of cedar pollinosis.

We also assessed the effects of antihistamines on the CNS. The psychometric tests used in this study have been shown to be valid and reliable measures in the evaluation of cognitive and psychomotor function impaired by sedative antihistamines and other psychoactive substances [9, 10, 31]. The various psychometric tests have been categorized according to their most relevant feature. Namely, Shamsi and Hindmarch [27] have proposed that CFF, CRT, CTT, RVIP, wrist actigraphy and LARS are useful as a means of measuring arousal, psychomotor-speed, sensorimotor co-ordination, attention, and physiological and subjective ratings, respectively.

A single oral administration of promethazine at 25 mg, which was used as a positive control, decreased the thresholds of CFF, increased recognition reaction time in the CRT, impaired tracking ability and the peripheral reaction in the CTT, decreased the correct response in the RVIP, and impaired the ratings of LARS used as a subjective assessment of sedation. The results suggest that promethazine produces significant impairments in cognitive and psychomotor function consistent with previous studies [9, 10, 26]. However, promethazine did not affect behavioral activity as measured by wrist actigraphy. Previous report has indicated that promethazine at 30 mg cause a reduction in daytime behavioral activity for up to 6 h [9]. It is not clear that such discrepancy in the results between wrist actigraphy and other psychomotor function. The wrist actigraphy provides a continuous measurement of behavioral activity, which is different from other psychomotor tests. Since a relaxed environment was offered to subjects when not being tested in waiting room to have them concentrate on other psychomotor tests in this study, the behavioral activity measured by the wrist actigraphy is influenced how subjects spend in the waiting room. It seems that the sedative effects induced by antihistamines was hard to measure by actigraphy, because the space of the waiting room was small, and most of subjects did not often move at there. Thus, the results of wrist actigraphy may be more prone to environmental factors than the other psychomotor tests.

In contrast to promethazine, fexofenadine (60 mg) and olopatadine (5 mg), the second-generation antihistamines, had no significant effect in any test when administered at their therapeutic doses. It has been reported that fexofenadine [17] and olopatadine [28] are selective histamine H_1 receptor antagonists. On the other hand, promethazine has the potent histamine and acetylcholine receptor antagonisms [1], which are related to the potent sedative effect of promethazine [15]. Fexofenadine did not have any disruptive effects on psychomotor or cognitive performance in healthy European volunteers, when administered at doses of up to 360 mg, in a double-blind, placebo-controlled

study with objective psychometric assessments [10]. On the other hand, we have reported that olopatadine at 10 mg, which is double the standard oral dose, caused a decrease in behavioral activity as measured by wrist actigraphy, although it did not affect other psychometric assessments [14]. In this study, olopatadine at 5 mg, however, did not cause the change in behavioral activity as measured by wrist actigraphy. The reason for discrepancy between the present result and the previous one may be due to the differences in dose used (single dose vs. double dose, respectively) or environmental factors when not being tested as mentioned above. These findings suggested that fexofenadine and olopatadine at the single therapeutic doses did not cause any cognitive or psychomotor dysfunction.

Recently, second-generation antihistamines have been further classified into two subgroups [12]; those that have no effect at the standard dose, and cause slight sedation at double the standard dose, as seen with cetirizine [38]; and those that do not induce sedation even at exceeded doses, as seen with fexofenadine [10, 38]. This classification is also supported by studies using PET, in which 0.1% of cerebral histamine H_1 receptors were occupied following treatment with fexofenadine at 120 mg (double the standard oral dose) [38], compared to 12.6 and 25.2% on treatment with cetirizine at 10 mg (a single dose) and 20 mg (a double dose), respectively [35]. Therefore, the dose-related brain penetration by cetirizine may have contributed to the dose-related cognitive impairment. It has been reported that the cerebral receptor occupancy by olopatadine at 5 mg is 15% [37], although studies of olopatadine at higher doses have not been done. Thus, olopatadine seems to belong to the same category as cetirizine. The therapeutic dose of olopatadine (single oral dose at 5 mg) is reasonably safe and suitable in terms of avoiding cognitive and psychomotor impairment, as shown in this study. In fact, olopatadine at 5 mg caused a marked improvement in nasal discharge and nasal congestion in Japanese patients with cedar pollinosis without increasing sleepiness and without decreasing attention [4].

Penetration of the blood–brain barrier is affected by various factors, such as lipophilicity, molecular size and number of hydrogen bonds. Recently, it has been proposed that the limited brain-penetrating capability of second-generation antihistamines may be the result of efflux from the CNS via the *p*-glycoprotein pump located at the blood–brain barrier. Since several second-generation antihistamines including fexofenadine [3] and olopatadine [18] are substrates for *p*-glycoprotein, *p*-glycoprotein-mediated efflux at the blood–brain barrier would result in low brain penetration of these compounds. However, it is unlikely that all second-generation antihistamines have equally low potential to cross the blood–brain barrier because it is possible that some of them modify *p*-glycoprotein efflux activity [19]. Olopatadine, like cetirizine [2], shows a certain amount of penetration, but not fexofenadine.

In conclusion, we found that olopatadine (5 mg) and fexofenadine (60 mg) did not cause any cognitive or psychomotor dysfunction in Japanese volunteers when administered at the therapeutic doses. This result is in contrast to the sedative effect of promethazine (25 mg), a first-generation antihistamine. Further, it is suggested that olopatadine would be a good therapeutic drug with the rapid and long-lasting effects for patients with peripheral histamine H_1 symptoms.

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